Advisory Committee Meeting

October 16, 2013

Vascepa (icosapent ethyl)

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Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

- Amarin is seeking approval of Vascepa as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo-B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent

- Pre-IND meeting in 2008
- Seeking approval for:
  - Treatment of severe hypertriglyceridemia (≥ 500 mg/dl)
    - Pancreatitis risk reduction
  - As add-on to statin therapy in subjects with mixed dyslipidemia and residually high TG levels (200 – 500 mg/dl)
    - Cardiovascular risk reduction

- Division agreed that a 12-week lipid-endpoint study could provide the basis for approval of Vascepa for the treatment of severe hypertriglyceridemia
- In 2012 the Division approved Vascepa for the treatment of severe hypertriglyceridemia based on data from the 12-week lipid-endpoint study MARINE

- Regarding the indication for Vascepa for use with a statin in subjects with TG levels of 200 – 500 mg/dl, the Division noted during the 2008 pre-IND meeting that there were no controlled clinical trial data demonstrating that the pharmacological reduction of TG levels with a second drug in patients with high TG at LDL-C goal on statin therapy significantly reduces the residual risk for cardiovascular disease
- Ongoing cardiovascular outcomes trials – e.g., ACCORD-Lipid, AIM-HIGH – would provide important information on the incremental benefit of adding a second lipid-altering drug to statin therapy

- Before accepting an application seeking approval of Vascepa as add-on to statin therapy in patients with elevated triglyceride levels (i.e., 200 – 500 mg/dl), Amarin would, at a minimum, have to provide the Division with the results from a 12-week lipid-endpoint study and have a cardiovascular outcomes trial up and running with at least 50% of subjects enrolled
- Special protocol assessment (SPA)
  - ANCHOR in 2009
  - REDUCE-IT in 2011

- Special protocol assessment (SPA)
  - FDA and company come to a written agreement on the design, size, and analyses of studies used to support approval of an efficacy claim
  - Considered binding unless it is determined that a substantial scientific issue essential to determining the safety or efficacy of the drug has been identified after the testing has begun
- Results from a number of cardiovascular outcomes trials that have bearing on today's discussion have been published in the past 2-3 years
  - ACCORD-Lipid, AIM-HIGH, HPS2-THRIVE, OM3FA

Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC)

October 16, 2013

ANCHOR: Clinical Review

Mary Dunne Roberts, MD
Medical Officer

Outline

- Clinical practice guidelines
- Regulatory history of VASCEPA
- ANCHOR trial design and results
- Putting ANCHOR in context
  - Effect of combination therapy on residual risk of CV events
  - Effect of Omega 3 Fatty Acids on risk of CV events
- Summary

Current lipoprotein/lipid management

- Primary goal – low-density lipoprotein (LDL-C) lowering
- Positive association with cardiovascular disease (CVD) risk
- Improvement in LDL-C – reduction in adverse cardiovascular (CV) outcomes
- Problem - residual risk of cardiovascular events persists
- Solution? - Modification of other risk factors (e.g. other lipoproteins, hypertension) may further mitigate risk
- Triglycerides (TG)
  - Associated with CVD – risk predictor or causal relationship?
  - Will drug-induced modulation of TG improve outcomes?

Guidelines	Primary target	TG level (mg/dL)	Treatment strategy
NCEP ATP III 2001	LDL-C	200-499	Reduce non-HDL-C Reduce weight, Increase physical activity Consider drug treatment (intensify LDL-C lowering or add fibrates, niacin to lower VLDL-C)

- Since 2001, various scientific associations have endorsed this approach-with caveats
- American Diabetes Association/American College of Cardiology Foundation Consensus Statement – Lipoprotein Management in Patients with Cardiometabolic Risk (2008)
  - " …there is not yet robust evidence for incremental benefits or risks of combination therapy compared with those of monotherapy. Results of ongoing and future trials of statin-niacin, statin-fibrate, and statin–[omega]n-3 fatty acids will, it is hoped, help answer these questions"

Marine-derived Omega-3 Fatty Acids (OM3FA)

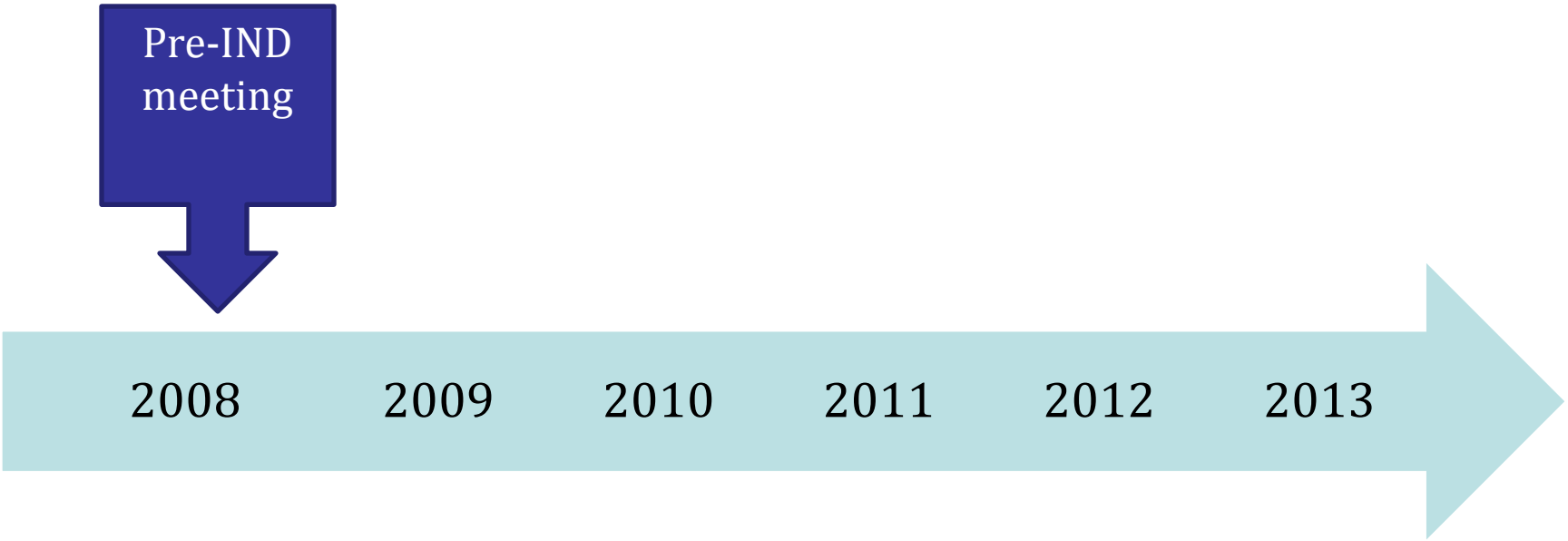
- Eicosapentaenoic acid (EPA)
- Docosahexaenoic acid (DHA)
- Available over-the-counter with variable quantities of EPA or DHA

Prescription Marine-derived OM3FA

- LOVAZA
  - Combination ethyl esters of OM3FA - EPA and DHA
  - 1 gram capsule contains 460 mg of EPA and 375 mg of DHA
  - Approved for treatment of severe hypertriglyceridemia (≥500 mg/dL) in 2004

- VASCEPA
  - Purified ethyl ester of EPA derived from fish oil
  - 1 gram capsule contains approximately 1 gram EPA
  - Approved for treatment of severe hypertriglyceridemia (HTG) in 2012

Regulatory history



Regulatory history

Pre-IND meeting

Discussed plans to pursue two patient populations

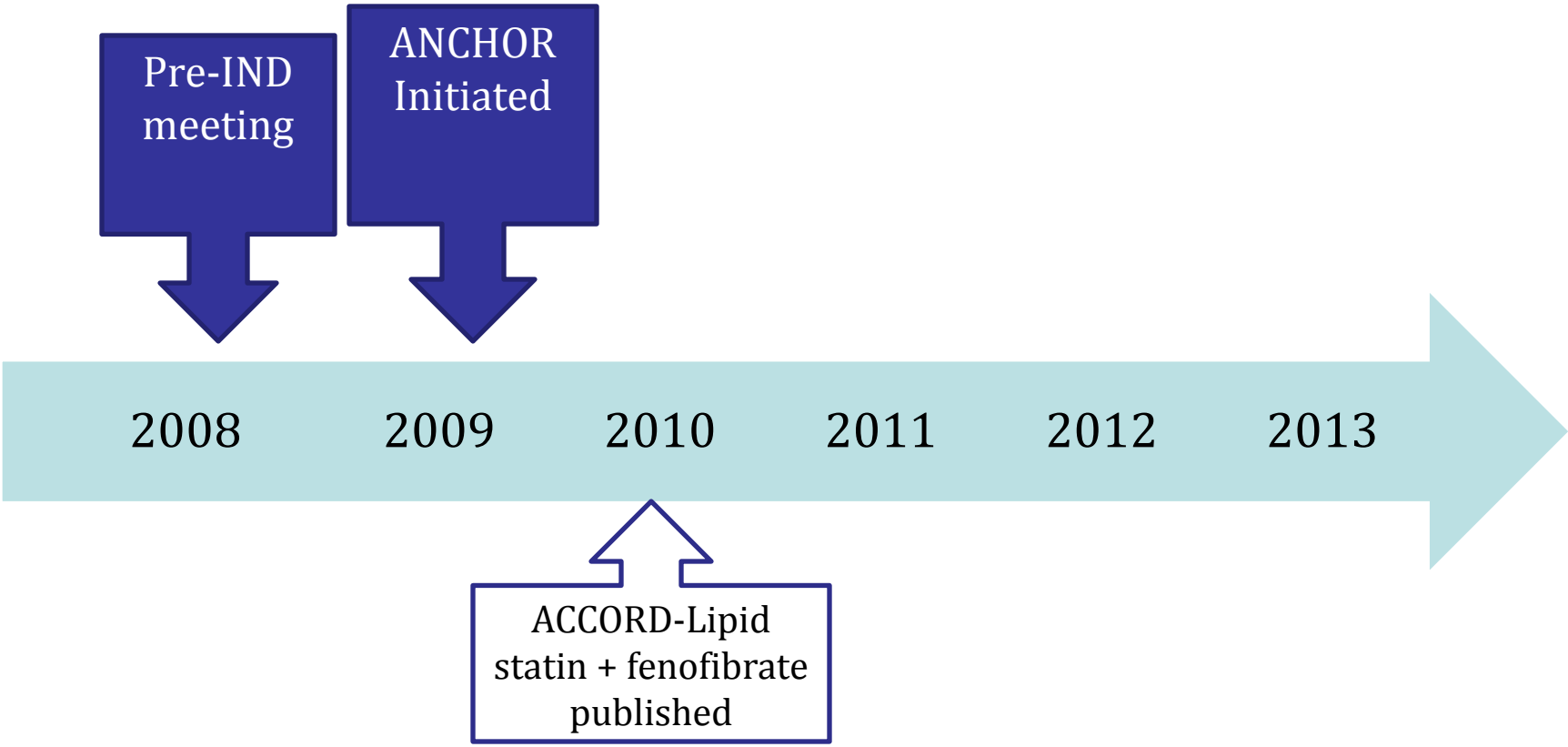
- Severe HTG (≥ 500 mg/dL)
- High TG (>200 mg/dL) not controlled by diet and statin

"The AIM-HIGH, ACCORD, and IMPROVE-IT studies…will provide important information on the incremental benefit of adding a second lipid-active drug to statin therapy."

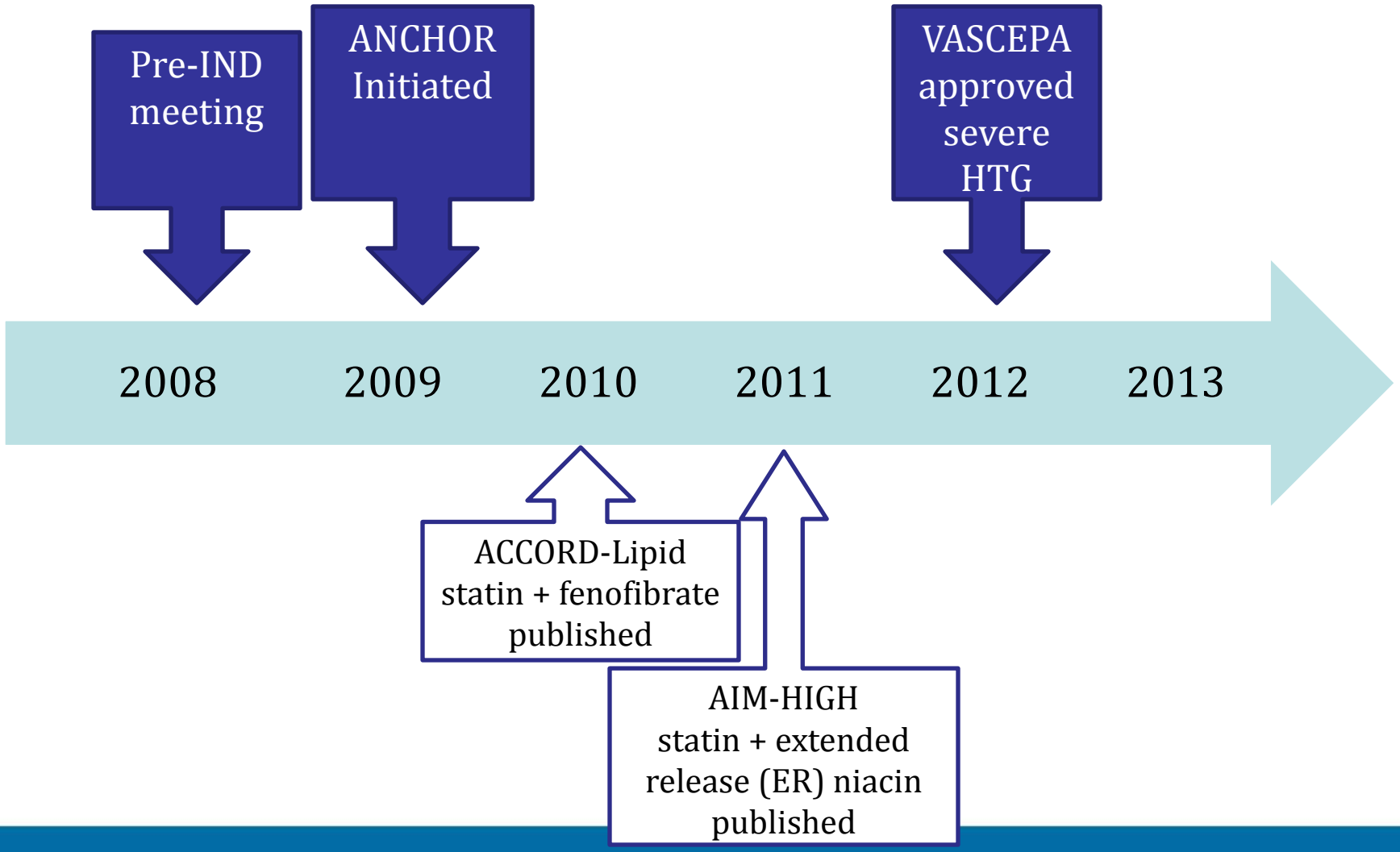
"At a minimum … provide results from 12-week study [with lipid endpoints]…and cardiovascular outcome trial (CVOT) needs to be well underway at the time of review of the 12-week study"

2008

Regulatory history



Regulatory history



Regulatory history

VASCEPA Approved July 2012

Pivotal efficacy trial: MARINE – 229 patients with severe HTG

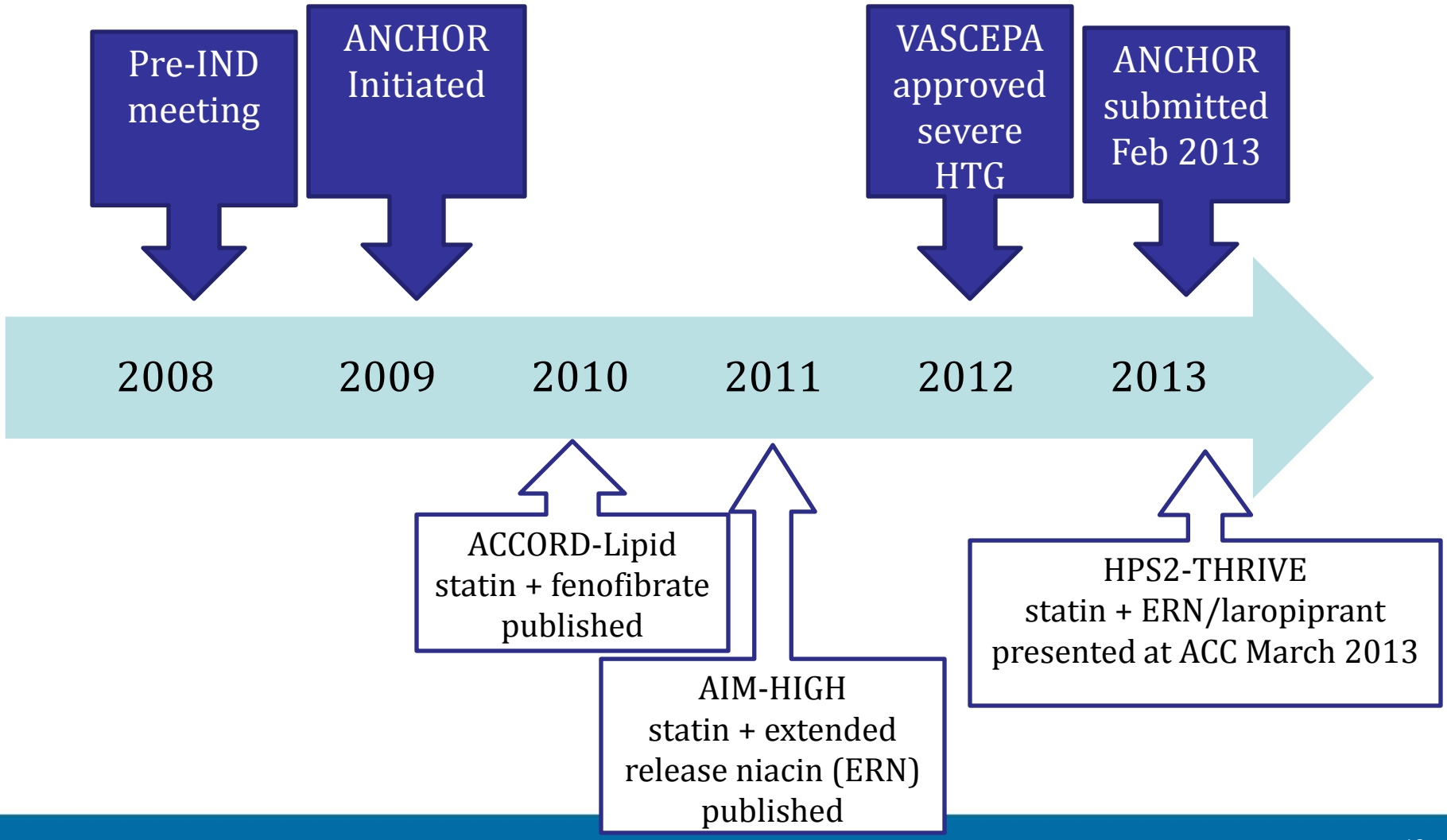
Treatment indication: VASCEPA 4g/day is indicated as an adjunct to diet to reduce TG in adult patients with severe hypertriglyceridemia (TG≥ 500 mg/dL)

Available in 1 gram capsules

Estimated 1.7% (3.4 million) of U.S. adults with severe TG

2012

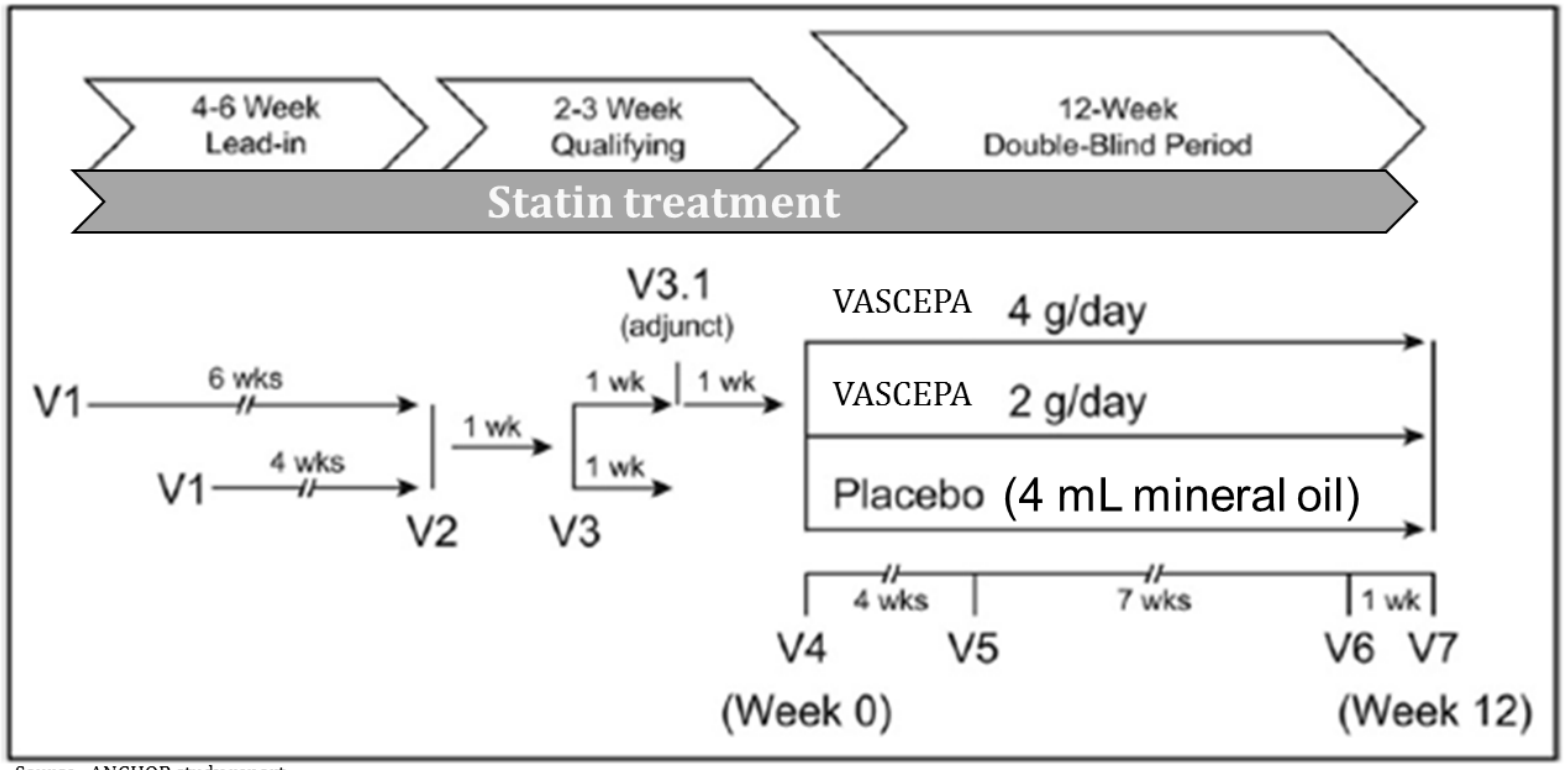
Regulatory history



Indication sought based on ANCHOR

- VASCEPA (4 grams/day) is indicated as an adjunct to diet in combination with a statin to reduce TG, non-HDL-C, Apo-B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent
  - CHD risk equivalents comprise
    - Diabetes
    - Atherosclerotic disease (e.g. peripheral arterial disease)
    - Multiple risk factors that confer a 10 year risk for CHD >20%
- Estimated 21% (42 million) of U.S. adults with mixed dyslipidemia
- Implied CV benefit in this indication

ANCHOR Study Design



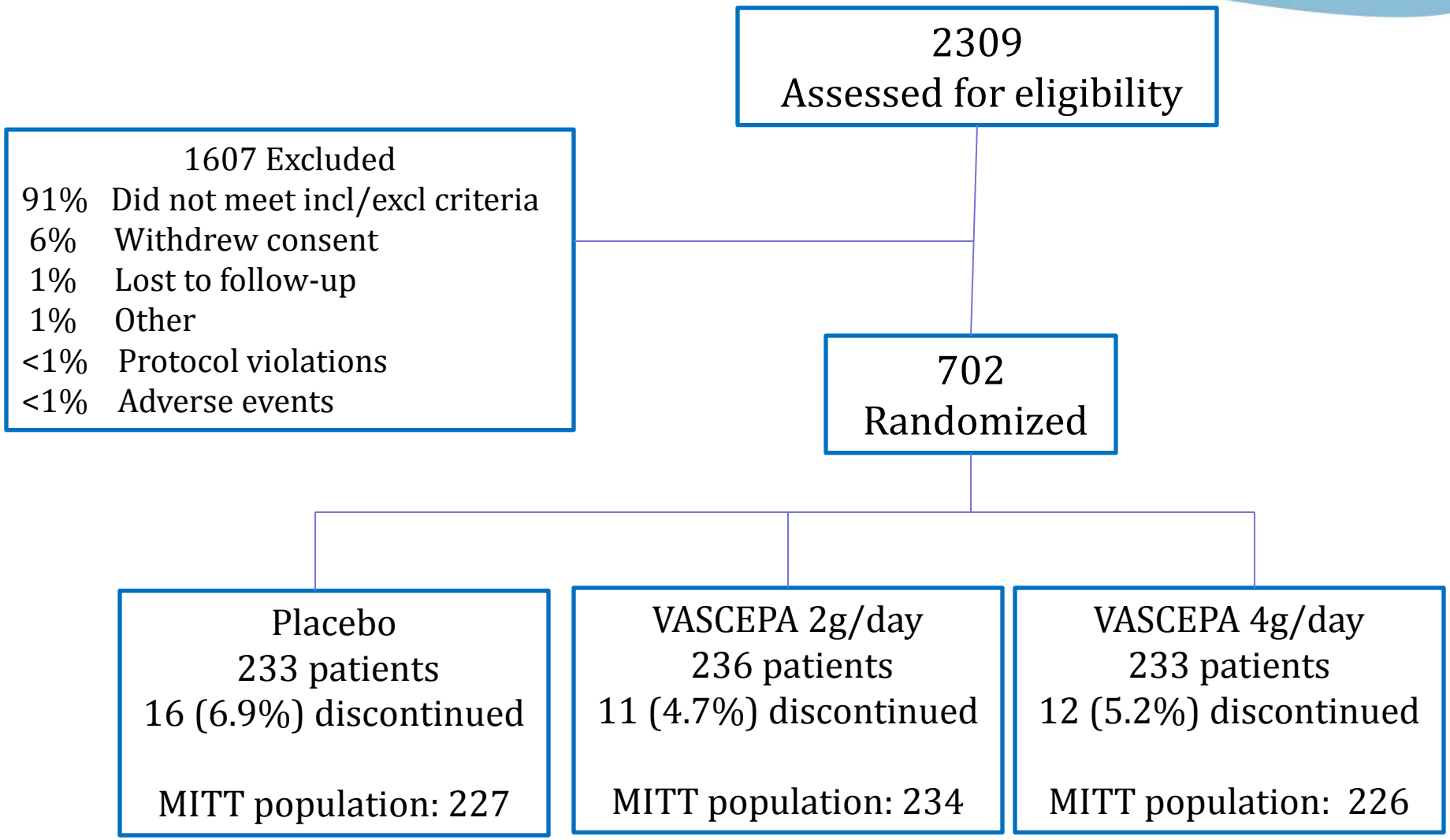
Source: ANCHOR study report

TG Baseline → TG Week 12 Endpoint

Average of Week 0 (V4) and previous measurement

Average of Week 11 (V6) and 12 (V7)

Disposition of Study Participants



Demographics and Medical History

Characteristic	Placebo N=233	VASCEPA 4g/day N=233
Males (%)	62	61
Age (years)	61	61
Race Caucasian (%) African American (%)	 96 <2	 97 <1
BMI (kg/m^2)	33	33
Diabetes (%)	73	73
HTN (%)	84	83
History of CV disease (%)	37	32

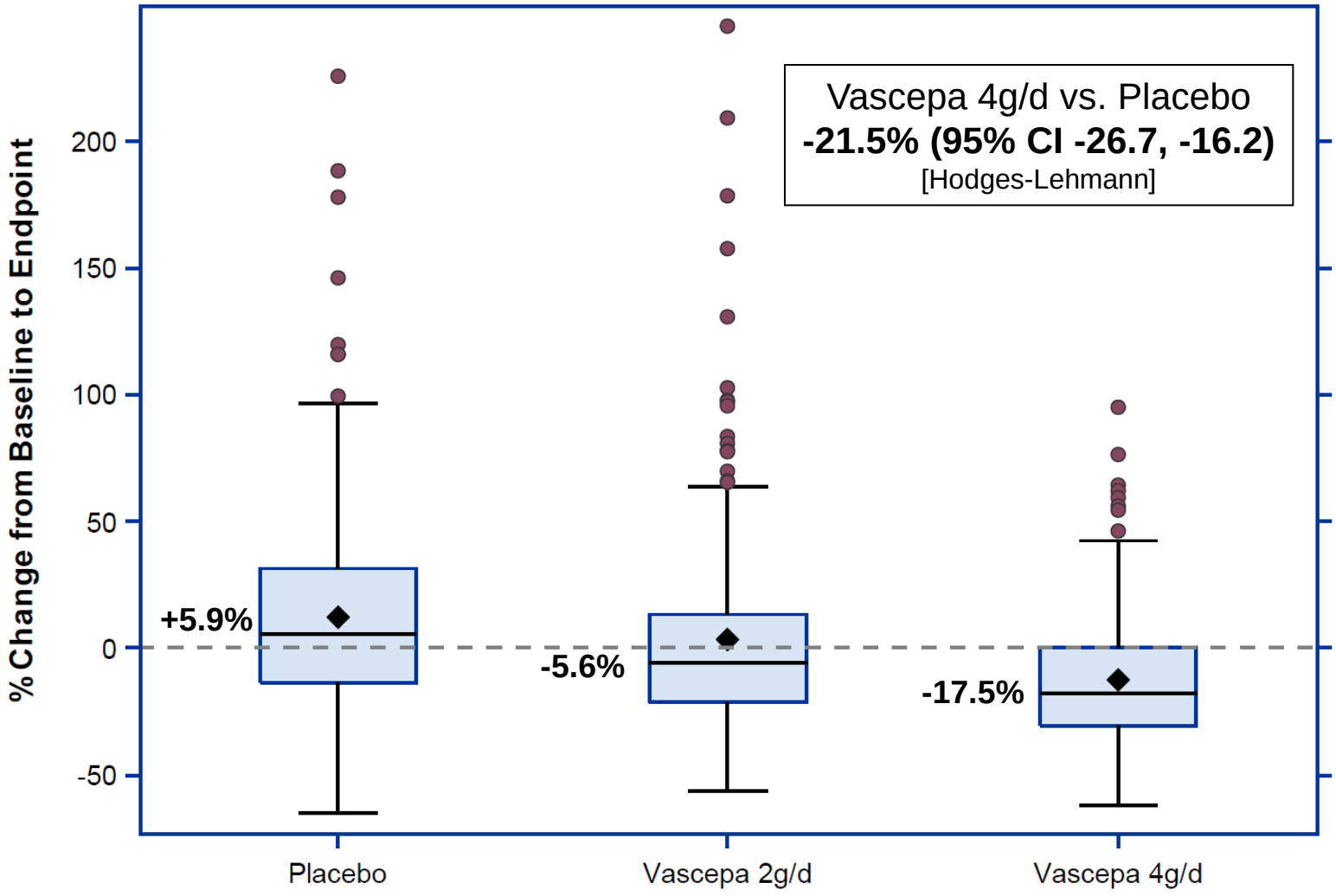
Randomized population

Median Baseline Values– Lipid/Lipoproteins

Endpoint hierarchy	Parameter	Placebo N=233	VASCEPA 4g/day N=233
Primary	TG (mg/dL)	258	268
Secondary	LDL-C (mg/dL)	84	82
	Non-HDL-C (mg/dL)	128	128
	VLDL-C (mg/dL)	42	45
	Apo B (mg/dL)	92	93
Exploratory (selected)	HDL-C (mg/dL)	39	37
	TC (mg/dL)	168	167

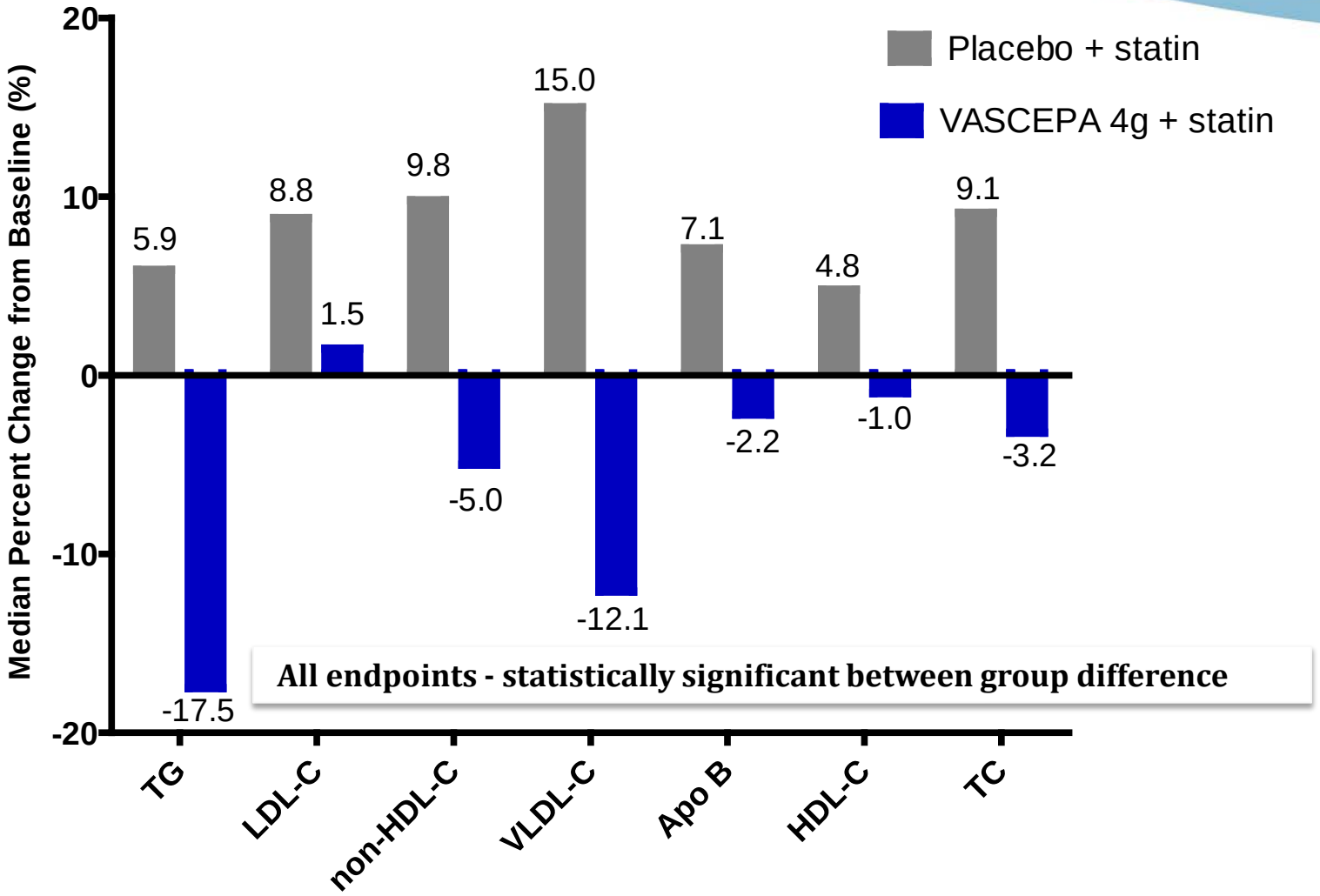
Randomized population

% Change in Triglycerides



One subject in Vascepa 4g/d group not shown (+564% change)

ANCHOR – Efficacy Week 12 Results



Mineral oil placebo

- ANCHOR trial placebo – mineral oil 2 mL twice a day
- Placebo-controlled trials – between group differences best estimate of treatment effects
- Assumes placebo is inert and no other factor is differentially affecting placebo-group versus the active-group
- Placebo group endpoint changes unfavorable, atypical
- Evaluated potential causes for changes
  - Randomization issues, unblinding, statin absorption, study design, placebo group lipid changes in other trials
  - Root cause uncertain
- Implications for REDUCE-IT trial?
  - attenuation of statin effect? - discussed with sponsor, relayed concern to data monitoring committee
- Implications for ANCHOR trial, if any?

- Possible implications of placebo group and ANCHOR results
  - None? – factors were equally distributed – true effect of treatment
  - Overestimation of treatment effect?

	Median % Change from Baseline to Week 12		**Median % Change (95% CI)**
	Placebo	VASCEPA 4g/d	Treatment difference
TG	+5.9	-17.5	-21.5 (-26.7, -16.2)
Direct LDL-C	+8.8	+1.5	-6.2 (-10.5, -1.7)
Non-HDL-C	+9.8	-5.0	-13.6 (-17.2, -9.9)
VLDL-C	+15.0	-12.1	-24.4 (-31.9, -17.0)
Apo B	+7.1	-2.2	-9.3 (-12.3,-6.1)
Total Cholesterol	+9.1	-3.2	-12.0 (-14.9, -9.2)
HDL-C	+4.8	-1.0	-4.5 (-7.4, -1.8)

Efficacy Summary

- In ANCHOR, 12 weeks of treatment with VASCEPA 4 grams/day led to a reduction in the primary efficacy endpoint, TG, compared with the mineral oil placebo, among statin-treated patients with mixed dyslipidemia at high cardiovascular risk

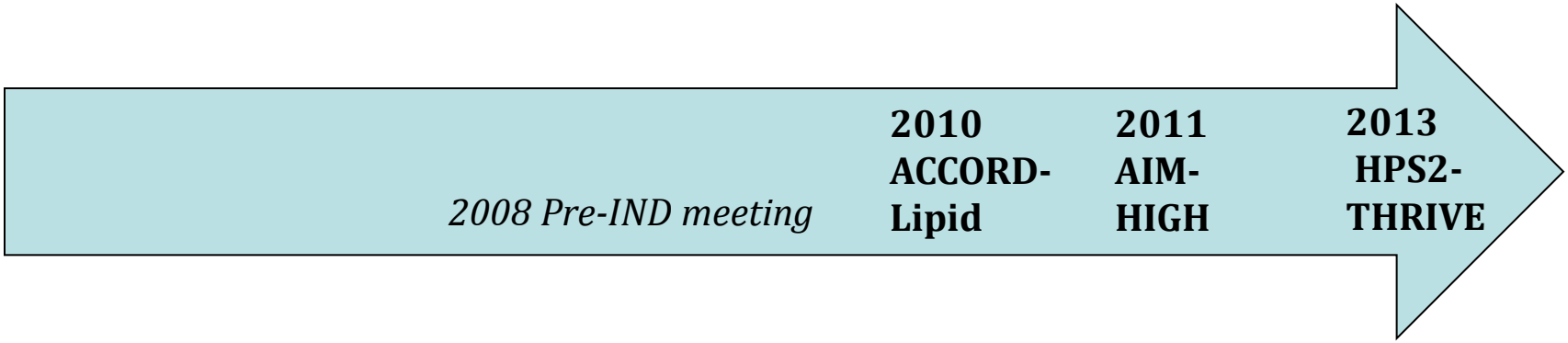
- The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo

- Other lipoprotein parameters (non-HDL-C, VLDL-C, Apo B) changed with VASCEPA treatment in a favorable direction

- Ultimately, will the observed changes in lipids/lipoproteins with VASCEPA treatment in statin-treated patients translate into a benefit on cardiovascular outcomes?

Clinical meaningfulness

- "Results of ongoing and future trials of statin-niacin, statin-fibrate, and statin–[omega]n-3 fatty acids will, it is hoped, help answer these questions"
  - » ADA/ACCF 2008 Consensus Statement



- Effect of add-on therapy to statins on cardiovascular events
  - 2010 ACCORD-Lipid – Fenofibrate
  - 2011 AIM-HIGH – ER niacin
  - 2013 HPS2-THRIVE – ER niacin/laropiprant

ACCORD-Lipid

- Randomized, double-blind, placebo-controlled add-on trial
- Simvastatin plus *fenofibrate* vs. simvastatin plus placebo
- Primary outcome: major cardiovascular events
  - CV death, Non-fatal (NF) myocardial infarction (MI), NF stroke
- 5518 patients with type 2 diabetes; Mean follow-up 4.7 years
- Baseline TG 162 mg/dL, HDL-C 38 mg/dL, LDL-C 101 mg/dL

% change from baseline to study end	Statin	Statin+Fenofibrate
TG	-9%	-22%
HDL-C	+6%	+8%
LDL-C	-21%	-19%

- No significant difference in primary outcome
  - HR=0.92 (95% CI 0.79-1.08; p=0.32)

AIM-HIGH

- Randomized, double-blind, placebo-controlled add-on trial
- Simvastatin plus *ER Niacin* vs. simvastatin plus placebo
- Primary outcome – CHD death, NF MI, stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization
- 3414 patients; Mean follow-up 3 years
- Baseline TG 161 mg/dL, HDL-C 35 mg/dL , LDL-C 71 mg/dL

% change from baseline (Two year visit)	Statin	Statin+ER Niacin
TG	-8%	-29%
HDL-C	+10%	+25%
LDL-C	-6%	-12%

- No significant difference in primary outcome
  - HR 1.02 (95% CI 0.87-1.21; p=0.80)

HPS2-THRIVE

- Randomized, double-blind, placebo-controlled add-on trial
- Simvastatin plus *ER Niacin/laropiprant* vs. simvastatin plus placebo
- Primary outcome: major vascular events - coronary death, NF MI, stroke, revascularization
- 25,673 patients at high cardiovascular risk
- Baseline TG 125 mg/dL, HDL-C 44 mg/dL, LDL 63 mg/dL

	Treatment difference (Effect of ER niacin/laropiprant)
TG	-33 mg/dL
HDL-C	+6 mg/dL
LDL-C	-10 mg/dL

- No significant difference in primary outcome
  - Risk ratio 0.96 (95% CI 0.90-1.03; p=0.29)

Summary – Add-on Statin Therapy CVOTs

- No conclusive evidence that additional modifications of non-LDL-C lipid/lipoproteins translate into further cardiovascular benefit in the setting of optimized statin therapy and LDL-C control in the overall populations studied
- ACCORD-Lipid, AIM-HIGH have suggested possible treatment benefit in certain patient subgroups (high TG, low HDL-C)
- However, this hypothesis has not been validated in prospective, randomized, placebo-controlled trials

Omega-3 Fatty Acid CVOTs

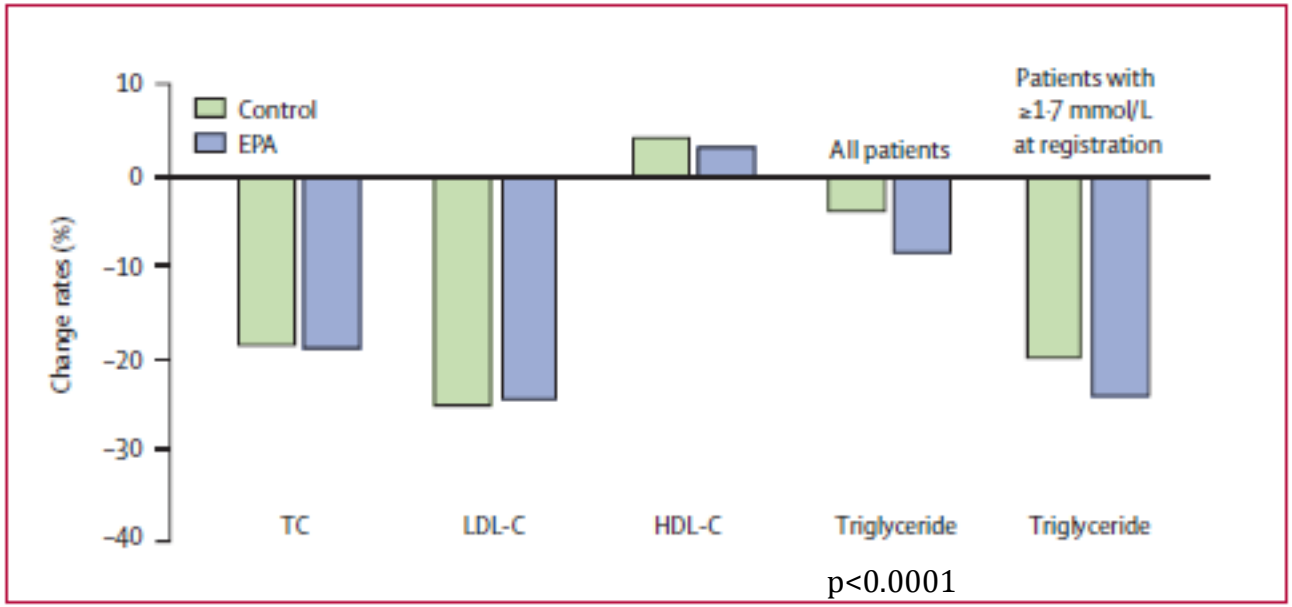
- 1980s – Diet and Reinfarction Trials (DART)
- Cardiovascular outcomes varied
- Many used ≤1 gram/day OM3FA
- Background therapy varied statin use 5 to 90% at baseline
- Event rates lower than expected

Study/Year published	Primary Outcome (CI)
GISSI-P/1999	RR=0.85 (0.74–0.98)
JELIS/2007	HR=0.81 (0.69-0.95)
GISSI-HF/2008	HR=0.91 (0.83-0.99)
OMEGA/2010	OR=0.95 (0.56-1.60)
Alpha-Omega/2010	HR=1.01 (0.87-1.17)
SU.FOL.OM3/2010	HR=1.08 (0.79-1.47)
ORIGIN/2012	HR=0.98 (0.87-1.10)
Risk & Prevention/2013	HR=0.98 (0.88-1.08)

JELIS: Statin + EPA Effect on Cardiovascular Outcomes

- 18,645 Japanese adults with elevated cholesterol (≥250 mg/dL) with or without coronary artery disease (CAD)
- Randomized to open-label treatment after 4-8 wk washout
  - EPA ethyl ester (1.8 grams/day) + pravastatin 10 mg or simvastatin 5 mg/day versus
  - Pravastatin 10 mg or simvastatin 5 mg/day (no placebo)
- 69% women, 61 years old, 36% HTN, 16% DM, 20% CAD
- LDL-C 182 mg/dL, TG 154 mg/dL (median)
- Primary endpoint: major coronary event – sudden cardiac death, fatal/NF MI, unstable angina, and cardiac bypass surgery/angioplasty

Lipid changes at study end (5 years) - JELIS



Only 5% treatment difference in TG between groups

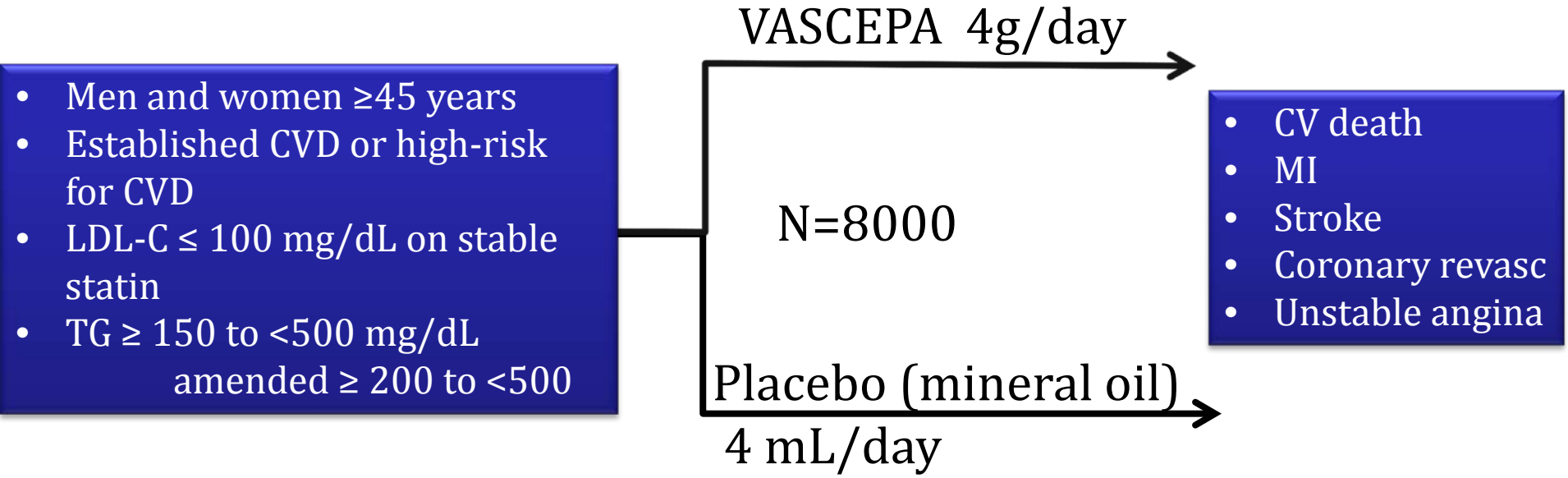
JELIS Primary Outcome – All Patients

	N	%	N	%		
Major coronary events	324	3.5	262	2.8	0.81 (0.69-0.95)	0.01
Sudden cardiac death	17	0.2	18	0.2	1.06 (0.55-2.07)	0.85
Fatal MI	14	0.2	11	0.1	0.79 (0.36-1.74)	0.56
Non-fatal MI	83	0.9	62	0.7	0.75 (0.54-1.04)	0.09
Unstable angina	193	2.1	147	1.6	0.76 (0.62-0.95)	0.01
CABG or PTCA	222	2.4	191	2.1	0.86 (0.71-1.05)	0.14

Limitations of JELIS study

- Patient population - Japanese, mostly women (69%), high baseline and on-treatment LDL-C – limits generalizability
- Low-dose statin as background therapy in JELIS
  - Average dose pravastatin 10.0 mg, simvastatin 5.6 mg
- Open-label design
  - Potential for bias
    - Influence on patient and physician behavior
      - Reporting of symptoms
      - Decisions regarding hospitalizations
      - Referral of events for adjudication

REDUCE-IT



- Study start November 2011
- Study duration 4 to 6 years
- 1612 events needed
- 90% power to detect 15% decrease in primary endpoint
- Expected placebo annual event rate 5.2%

Summary

- Treatment with 12 weeks of VASCEPA 4g/day vs. mineral oil placebo demonstrated statistically significant improvement in TG and other lipids/lipoproteins in statin-treated patients
- Recent cardiovascular outcome trials with fenofibrate and niacin call into question whether targeting lipids/lipoproteins other than LDL-C yield incremental CV benefit in the setting of contemporary statin therapy
- Cardiovascular outcome trials with Omega-3 Fatty Acids do not consistently support benefit
- Thus, whether the lipid changes, specifically TG (and non-HDL-C), observed in the ANCHOR study will translate into lower rates of major adverse cardiovascular events is debatable
- REDUCE-IT – will assess whether treatment with VASCEPA improves clinical outcomes among statin-treated patients with residually elevated TG